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Original Contributions

Ambulatory Pulse Pressure as Predictor of Outcome in Older Patients With Systolic Hypertension

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We enrolled 808 older patients with isolated systolic hypertension (160 to 219/71 <95 mm Hg) to investigate whether ambulatory measurement of pulse pressure and mean pressure can refine risk stratification. The patients (≥60 years) were randomized to nitrendipine (10 to 40 mg/day) with the possible addition of enalapril (5 to 20 mg/day) or hydrochlorothiazide (12.5 to 25 mg/day) or to matching placebos. At baseline, pulse pressure and mean pressure were determined from six conventional blood pressure (BP) readings and from 24-h ambulatory recordings. With adjustment for significant covariables, we computed mutually adjusted relative hazard rates associated with 10 mm Hg increases in pulse pressure or mean pressure. In the placebo group, the 24-h and nighttime pulse pressures consistently predicted total and cardiovascular mortality, all cardiovascular events, stroke, and cardiac events. Daytime pulse pressure predicted cardiovascular mortality, all cardiovascular end points, and stroke. The hazard rates for 10 mm Hg increases in pulse pressure ranged from 1.25 to 1.68. Conventionally measured pulse pressure predicted only cardiovascular mortality with a hazard rate of 1.35. In the active treatment group compared with the placebo patients, the relation between outcome and ambulatory pulse pressure was attenuated to a nonsignificant level. Mean pressure determined from ambulatory or conventional BP measurements was not associated with poorer prognosis. In conclusion, in older patients with isolated systolic hypertension higher pulse pressure estimated by 24-h ambulatory monitoring was a better predictor of adverse outcomes than conventional pulse pressure, whereas conventional and ambulatory mean pressures were not correlated with a worse outcome. Am J Hypertens 2002;15:835–843 © 2002 American Journal of Hypertension, Ltd.

Key Words: Ambulatory blood pressure monitoring, hypertension, mean pressure, morbidity, mortality, prognosis, pulse pressure.

Current guidelines for the management of hypertension rest almost completely on systolic and diastolic blood pressure (BP), two specific inflection points of the BP wave.[1] However, BP propagates through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component (pulse pressure) and a steady component (mean pressure).[2] The former depends on ventricular ejec-

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A list of Syst-Eur Trial participants is given in the Appendix.

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Table 1. Blood pressure at randomization in 808 patients

Blood Pressure Measurement	Systolic Pressure	Diastolic Pressure	Pulse Pressure	Mean Pressure
Conventional pressure (mm Hg)*	173.3 ± 10.8	86.0 ± 5.8	87.3 ± 12.1	115.2 ± 5.5
24-h pressure (mm Hg)	145.8 ± 15.6	79.3 ± 8.9	66.5 ± 13.3	102.3 ± 10.1
Daytime (from 10 to 20 h) pressure (mm Hg)	151.4 ± 16.2	84.1 ± 9.8	67.3 ± 13.9	107.1 ± 10.7
Nighttime (from midnight to 6 h) pressure (mm Hg)	134.0 ± 18.6	70.2 ± 10.1	63.8 ± 14.7	92.2 ± 11.9

Values are means ± SD.
* Mean of six readings, ie, two obtained at each of three run-in visits.

tion, arterial stiffness, and the timing of the wave reflections in the arterial tree,[3] whereas cardiac output and peripheral vascular resistance are the major determinants of mean pressure.[2] Observational studies[4–10] and recent overviews,[11] all based on the calculation of pulse pressure and mean pressure from conventional BP readings, suggested that in middle-aged and older subjects cardiovascular prognosis gets worse with higher pulse pressure, not mean pressure. Until now, few studies[12,13] addressed the question whether the use of ambulatory pulse pressure or ambulatory mean pressure may further enhance the risk stratification of hypertensive patients. In this article, we used the ambulatory BP recordings obtained in the Systolic Hypertension in Europe (Syst-Eur) Trial[14] to investigate whether ambulatory pulse pressure is a better predictor of outcome than ambulatory mean pressure or than pulse pressure or mean pressure calculated from conventional BP readings.

Methods

The protocol of the Syst-Eur trial, described elsewhere,[15] was approved by the Ethics Committees of all participating centers. Eligible patients were at least 60 years old and had, when seated, a systolic pressure of 160 to 219 mm Hg, with a diastolic pressure less than 95 mm Hg. These BP criteria rested on the mean of six conventional readings obtained in the sitting position during the placebo run-in period (two readings at three visits 1 month apart). The patients were randomly assigned double-blind treatment with active medication or placebo. The study medications were titrated and combined to reduce the systolic pressure by 20 mm Hg or more to below 150 mm Hg (average of two readings at each follow-up visit). Active treatment started with nitrendipine[16] (10 to 40 mg/day). If necessary, the calcium-channel blocker was combined with or replaced by enalapril (5 to 20 mg/day), hydrochlorothiazide (12.5 to 25 mg/day), or both drugs. In the placebo group, matching placebos were used in a similar way.

Forty-six of 198 Syst-Eur centers opted to enroll all their patients in the study.[17] Validated[18] monitors were programmed to obtain measurements at intervals no longer than 30 min. The cuff was secured to the nondominant arm, except if on conventional sphygmomanometry, the difference in systolic pressure between both arms was 10 mm Hg or more, in which case the arm giving the highest reading was chosen for all BP measurements. If arm circumference exceeded 31 cm, cuffs with 35- by 15-cm bladder were used.

Of 837 randomized patients with a 24-h ambulatory recording at baseline, 29 (3.5%) were excluded because more than 20% of the required readings were unavailable. Of the remaining 808 patients,[17] 695[19] underwent their baseline recording during the run-in phase of the trial and 113 shortly after randomization (median, 4 months; interquartile range, 2 to 5 months). From unedited recordings, we computed time-weighted BP means for the entire day, daytime (from 10:00 to 20:00) and nighttime (from midnight to 06:00).[17] Pulse pressure was defined as systolic minus diastolic BP. Ambulatory mean pressure was measured oscillometrically in 668 patients (82.7%). For auscultatory readings obtained by ambulatory monitoring or conventional BP measurement, mean pressure was computed as diastolic pressure plus one-third of pulse pressure.

We based our statistical analysis on an intention-to-treat principle and two-sided tests, using SAS software version 8.01 (Cary, NC). Means were compared by the standard normal z-test[20] and proportions by the χ^2 statistic. We used Pearson's correlation coefficients and partial correlation coefficients to study the association between pulse pressure, pulse rate, and body height. We calculated relative hazard rates and modeled the probability of the 2-year incidence of end points by multiple Cox regression adjusted for significant covariates, including sex, age, previous cardiovascular complications, and current smoking. We used Wald's χ^2 statistic to compare the strength of associations.

Results

Patients Characteristics at Baseline

Mean (SD) age was 69.6 (6.2) years. At baseline, the placebo ($n = 393$) and active treatment ($n = 415$) groups had similar characteristics, including all types of BP measurement (Table 1). Body mass index averaged 26.1 (3.2) kg/m^2 in 311 men and 27.0 (4.4) kg/m^2 in 497 women. Previous cardiovascular complications were present in 215 patients, of whom 119 had a Sokolow-Lyon voltage index

Table 2. Changes in blood pressure at last available ambulatory recording

Blood Pressure Measurement	Systolic Pressure	Diastolic Pressure	Pulse Pressure	Mean Pressure
Placebo (n = 265)*				
Conventional (mm Hg)	12.8 ± 19.6	3.8 ± 9.3	8.9 ± 16.9	6.8 ± 11.1
24-h (mm Hg)	2.1 ± 13.6	2.6 ± 8.1	−0.5 ± 10.5	1.3 ± 9.6
Daytime (mm Hg)	3.7 ± 16.6	3.6 ± 9.7	0.1 ± 13.1	2.4 ± 11.5
Nighttime (mm Hg)	0.0 ± 14.2	1.3 ± 9.0	−1.3 ± 10.3	−0.3 ± 10.6
Active treatment (n = 271)*				
Conventional (mm Hg)	23.5 ± 19.0	8.0 ± 9.6	15.5 ± 16.5	13.1 ± 11.0
24-h (mm Hg)	10.7 ± 13.8	6.4 ± 8.5	4.3 ± 10.0	5.8 ± 13.5
Daytime (mm Hg)	11.2 ± 14.7	7.0 ± 10.2	4.3 ± 11.4	6.5 ± 14.5
Nighttime (mm Hg)	9.7 ± 18.1	5.4 ± 10.2	4.3 ± 11.8	4.8 ± 15.3
Effect of treatment (n = 536)†				
Conventional (mm Hg)	10.6 (7.4–13.9)	4.2 (2.6–5.8)	6.6 (3.8–9.4)	6.4 (4.5–8.3)
24-h (mm Hg)	8.5 (6.2–10.8)	3.8 (2.4–5.2)	4.8 (3.0–6.5)	4.5 (2.5–6.5)
Daytime (mm Hg)	7.5 (4.8–10.1)	3.4 (1.8–5.1)	4.2 (2.1–6.2)	4.0 (1.8–6.3)
Nighttime (mm Hg)	9.7 (6.9–12.4)	4.1 (2.5–5.8)	5.5 (3.7–7.4)	5.1 (2.9–7.3)

* Blood pressure differences (SD) in patients reassessed after randomization (value at follow-up subtracted from measurement at entry).
† Net effects (95% confidence interval) were calculated by subtracting the reduction in the placebo group from that in the active treatment group.

compatible with left ventricular hypertrophy, 344 (42.6%) had been treated with antihypertensive drugs before enrollment, 69 (8.5%) were current smokers, and 124 (15.3%) had consumed at least one glass of beer, wine, or liquor per day.

In 808 patients pulse pressure at baseline was inversely correlated with body height. For conventional, 24-h, daytime, and nighttime pulse pressures, the correlation coefficients ($P \leq .01$) were −0.225, −0.130, −0.096, and −0.146, respectively. After adjustment for sex and age, the respective partial correlation coefficients ($P \leq .01$) were similar. The correlations between pulse pressure and pulse rate were significant for 24-h (−0.070; $P = .045$) and daytime (−0.108; $P = .002$) measurements, but not for conventional (0.021; $P = .54$) and nighttime (−0.001; $P = .99$) measurements.

Treatment and BP During Follow-Up

The median follow-up in the 808 patients was 4.4 years. The number of patient-years in the placebo and active treatment groups amounted to 1666 and 1742, respectively. Of the 808 patients, 265 in the placebo group and 271 in the active treatment group underwent a reassessment of their conventional and ambulatory BP after randomization. At the last follow-up visit, 214 patients randomized to placebo and 243 allocated active treatment were still on double-blind medication (80.8% *v* 89.7%; $P = .004$), whereas 51 and 28 patients were in open follow-up (19.2% *v* 10.3%). Of the actively treated patients, 213 (87.7%) were taking nitrendipine (mean daily dose, 27.7 mg), 75 (30.9%) were on enalapril (14.0 mg), and 47 (19.3%) on hydrochlorothiazide (22.6 mg). The treatment-induced reductions in pulse pressure and mean pressure were 6.6 mm Hg and 6.4 mm Hg for the conventional BP, and 4.8 mm Hg and 4.5 mm Hg for the 24-h ambulatory pressure (Table 2).

Pulse Pressure and Mean Pressure as Risk Predictors

In multiple Cox regression we mutually adjusted the relative hazard rates associated with 10 mm Hg increases in pulse pressure for mean pressure (Table 3) and vice versa (Table 4). In these analyses, we also allowed for sex, age, previous cardiovascular complications, and current smoking. In the placebo group, the risk of cardiovascular mortality, all cardiovascular events, and fatal and nonfatal stroke increased with higher 24-h, daytime, and nighttime pulse pressures. For these outcomes, the hazard rates in relation to the ambulatory pulse pressures ranged from 1.56 to 1.68 ($P < .01$), from 1.25 to 1.38 ($P < .05$), and from 1.51 to 1.53 ($P < .05$), respectively (Table 3). In the placebo group, the 24-h and nighttime pulse pressures were also associated with an approximately 30% higher risk of total mortality and cardiac end points. The latter included fatal and nonfatal myocardial infarction, fatal and nonfatal congestive heart failure, and sudden death. In the placebo group, a 10 mm Hg higher conventional pulse pressure was only marginally associated with cardiovascular mortality, all cardiovascular events, and all strokes with hazard rates amounting to 1.35 ($P = .03$), 1.19 ($P = .06$), and 1.26 ($P = .08$), respectively. The incidence of cardiovascular events remained significantly associated with the 24-h ($P = .03$) or nighttime ($P = .02$) pulse pressure in Cox models, which also included conventional pulse pressure as independent explanatory variable.

In the active treatment group, in comparison with the patients randomized to placebo, the relation between outcome and ambulatory pulse pressure was attenuated (Table 3).

Table 3. Relative hazard rates associated with a 10 mm Hg increase in pulse pressure

	Mortality		Fatal and Nonfatal End Points		
	Total	**Cardiovascular**	**Cardiovascular**	**Stroke**	**Cardiac**
Placebo group					
Number of end points	39	22	54	20	35
Conventional pulse pressure	1.15 (0.94–1.42)	1.35 (1.03–1.76)†	1.19 (0.99–1.43)*	1.26 (0.97–1.65)*	1.11 (0.88–1.42)
24-h pulse pressure	1.28 (1.00–1.65)†	1.68 (1.24–2.28)§	1.34 (1.10–1.63)‡	1.53 (1.09–2.15)†	1.23 (0.96–1.57)
Daytime pulse pressure	1.19 (0.94–1.49)	1.56 (1.18–2.05)‡	1.25 (1.04–1.51)†	1.51 (1.09–2.08)†	1.14 (0.91–1.43)
Nighttime pulse pressure	1.33 (1.04–1.69)†	1.66 (1.23–2.26)‡	1.38 (1.13–1.67)‡	1.51 (1.09–2.10)†	1.31 (1.03–1.66)†
Active treatment group					
Number of end points	29	14	44	10	34
Conventional pulse pressure	1.03 (0.75–1.41)	1.20 (0.79–1.82)	1.16 (0.92–1.46)	1.36 (0.87–2.13)	1.11 (0.84–1.47)
24-h pulse pressure	1.06 (0.77–1.47)	1.41 (0.92–2.15)	1.26 (0.97–1.63)*	1.55 (0.91–2.66)	1.17 (0.87–1.57)
Daytime pulse pressure	1.07 (0.81–1.41)	1.35 (0.94–1.95)	1.16 (0.93–1.45)	1.28 (0.82–1.99)	1.12 (0.86–1.45)
Nighttime pulse pressure	1.01 (0.74–1.36)	1.28 (0.85–1.92)	1.28 (1.02–1.62)†	1.65 (0.98–2.79)*	1.17 (0.89–1.52)
Both treatment groups					
Number of end points	68	36	98	30	69
Conventional pulse pressure	1.11 (0.94–1.31)	1.29 (1.04–1.61)†	1.18 (1.03–1.35)†	1.30 (1.04–1.61)†	1.10 (0.92–1.30)
24-h pulse pressure	1.19 (0.98–1.45)*	1.55 (1.21–1.98)§	1.29 (1.11–1.51)‡	1.48 (1.14–1.93)‡	1.20 (0.99–1.45)*
Daytime pulse pressure	1.11 (0.93–1.33)	1.45 (1.16–1.81)‡	1.19 (1.04–1.37)†	1.35 (1.06–1.72)†	1.12 (0.95–1.33)
Nighttime pulse pressure	1.18 (0.98–1.42)*	1.47 (1.16–1.85)‡	1.32 (1.14–1.53)‡	1.50 (1.16–1.93)§	1.24 (1.04–1.48)†

Relative hazard rates (95% confidence interval) reflect the risk associated with a 10 mm Hg increase in pulse pressure. The hazard rates are adjusted for mean pressure, sex, age, previous cardiovascular complications, current smoking status, and if both treatment groups are combined also for active treatment.

Significance levels are indicated: * $.1 < P < 0.5$ (P value between .1 and .05); † $P \leq .05$; ‡ $P \leq .01$; and § $P \leq .001$.

Table 4. Relative hazard rates associated with a 10 mm Hg increase in mean pressure

	Mortality		Fatal and Nonfatal End Points		
	Total	**Cardiovascular**	**Cardiovascular**	**Stroke**	**Cardiac**
Placebo group					
Number of end points	39	22	54	20	35
Conventional mean pressure	1.19 (0.69–2.06)	0.86 (0.44–1.71)	0.75 (0.48–1.16)	0.99 (0.50–1.96)	0.82 (0.46–1.47)
24-h mean pressure	1.14 (0.86–1.50)	1.02 (0.70–1.48)	1.11 (0.88–1.40)	1.16 (0.79–1.72)	1.08 (0.81–1.45)
Daytime mean pressure	1.19 (0.91–1.55)	1.05 (0.73–1.51)	1.14 (0.91–1.43)	1.33 (0.93–1.92)	1.07 (0.80–1.43)
Nighttime mean pressure	1.12 (0.85–1.48)	1.10 (0.76–1.60)	1.15 (0.92–1.43)	0.95 (0.64–1.42)	1.21 (0.92–1.59)
Active treatment group					
Number of end points	29	14	44	10	34
Conventional mean pressure	1.89 (1.01–3.56)†	1.42 (0.64–3.16)	1.09 (0.68–1.75)	0.92 (0.33–2.57)	1.20 (0.70–2.08)
24-h mean pressure	1.06 (0.69–1.65)	0.67 (0.36–1.26)	0.92 (0.65–1.30)	0.80 (0.34–1.87)	1.00 (0.69–1.47)
Daytime mean pressure	0.81 (0.53–1.24)	0.63 (0.36–1.11)	0.83 (0.60–1.14)	0.57 (0.26–1.22)	0.92 (0.64–1.32)
Nighttime mean pressure	1.20 (0.88–1.64)	0.87 (0.53–1.44)	0.99 (0.75–1.31)	1.07 (0.56–2.04)	1.02 (0.75–1.39)
Both treatment groups					
Number of end points	68	36	98	30	69
Conventional mean pressure	1.46 (0.97–2.19)*	1.07 (0.64–1.78)	0.89 (0.65–1.21)	0.94 (0.55–1.62)	1.02 (0.69–1.50)
24-h mean pressure	1.15 (0.92–1.43)	0.93 (0.68–1.28)	1.04 (0.86–1.26)	1.14 (0.82–1.59)	1.05 (0.84–1.32)
Daytime mean pressure	1.08 (0.87–1.34)	0.92 (0.68–1.24)	1.02 (0.85–1.22)	1.16 (0.85–1.60)	1.01 (0.81–1.26)
Nighttime mean pressure	1.17 (0.96–1.43)	1.02 (0.77–1.37)	1.08 (0.91–1.28)	1.05 (0.77–1.44)	1.11 (0.91–1.36)

Relative hazard rates (95% confidence interval) reflect the risk associated with a 10 mm Hg increase in mean pressure. The hazard rates are adjusted for pulse pressure, sex, age, previous cardiovascular complications, current smoking status, and if both treatment groups are combined also for active treatment.

Significance levels are indicated: * $.1 < P < .05$ (P value between .1 and .05); † $P \leq .05$.

Table 5. Relative hazard rates for elevated Sokolow-Lyon Voltage index associated with pulse pressure or mean pressure

	Pulse Pressure (+10 mm Hg)	Mean Pressure (+10 mm Hg)
Number of cases in both treatment groups combined	53	53
Conventional pressure	1.12 (0.90–1.41)	1.27 (0.77–2.10)
24-h pressure	1.38 (1.10–1.74)†	1.06 (0.79–1.43)
Daytime pressure	1.28 (1.04–1.56)*	1.02 (0.78–1.33)
Nighttime pressure	1.45 (1.17–1.80)†	1.00 (0.78–1.30)

The relative hazard rates for pulse pressure and mean pressure are mutually adjusted and also account for sex, age, body mass index, and randomization to active treatment.

Significance levels are indicated: * $P \leq .05$ and † $P \leq .01$.

Only the relative hazard rate relating all cardiovascular events to the nighttime pulse pressure remained formally significant (1.28, $P = .03$). The results in all patients with additional adjustment for active treatment, in general, mirrored those observed in the placebo group (Table 3).

Mean pressure, both before and after adjustment (Table 4) for pulse pressure, did not behave as a significant predictor of outcome. The only significant association was in the patients on active treatment, in whom a 10 mm Hg higher conventional mean pressure at entry was correlated with a 89% higher risk of all-cause mortality (Table 4). Wald's χ^2 statistic showed that the relative hazard rates were lower for mean pressure than for pulse pressure (Tables 3 and 4) for conventional measurements in relation to all cardiovascular events (placebo group, 0.75 *v* 1.19 [$P = .06$]), for the 24-h BP in relation to cardiovascular mortality (placebo group, 1.02 *v* 1.68 [$P = .07$]; active treatment group, 0.67 *v* 1.41 [$P = .08$]; both treatment groups 0.93 *v* 1.55 [$P = .02$]), and for daytime pressure in relation to cardiovascular mortality (active treatment group 0.63 *v* 1.35 [$P = .05$]; both treatment groups 0.92 *v* 1.45 [$P = .03$]).

We obtained similar results, if the analyses were confined to the 695 patients[19] who had their baseline ambulatory BP recorded before randomization, if for all patients ambulatory mean pressure was computed as diastolic pressure plus one-third of pulse pressure, or if the Cox models were additionally adjusted for pulse rate and body height.

Sokolow-Lyon Voltage Index

Of 722 patients who had at least one electrocardiogram during follow-up, 110 showed at entry a Sokolow-Lyon voltage index compatible with left ventricular hypertrophy (≥3.5 mV). Among 612 patients with lower electrocardiographic voltages at baseline, 10.2% (30/294) of the placebo group and 7.2% (23/318) of the active treatment group attained during follow-up a Sokolow-Lyon index of 3.5 mV or more (Table 5). The number of patient-years in the placebo and active treatment groups amounted to 886 and 956, respectively. In Cox regression, we adjusted for sex, age, body mass index, and randomization to active treatment. With adjustment for these covariables, the mutually adjusted relative hazard rates were significant for all types of ambulatory pulse pressures, but not for the conventionally measured pulse pressure nor for mean pressure regardless of the technique of measurement (Table 5).

Risk Associated With 24-Hour Systolic and Diastolic BP

In multiple Cox regression, we introduced the 24-h systolic and diastolic pressures at entry as explanatory variables together with sex, age, previous cardiovascular complications, current smoking, and randomization to active treatment. For cardiovascular mortality (Fig. 1), the relative hazard rates associated with 10 and 5 mm Hg increases in the 24-h systolic and diastolic pressures were 1.49 (95% confidence interval, 1.17–1.89, $P = .001$) and 0.51 (0.34–0.77; $P = .001$). For all cardiovascular end points, these estimates were 1.31 (1.12–1.52; $P < .001$) and 0.74 (0.58–0.95; $P = .02$), respectively. These findings highlight the importance of ambulatory pulse pressure as cardiovascular risk factor. At any given level of 24-h systolic pressure, a lower 24-h diastolic pressure was associated with a worse cardiovascular prognosis.

Discussion

In untreated older patients with systolic hypertension, higher ambulatory pulse pressure increased the risk of total and cardiovascular mortality and that of cardiovascular complications, whereas the conventionally measured pulse pressure predicted only cardiovascular mortality. The 24-h and nighttime ambulatory pulse pressures predicted cardiovascular outcome over and beyond pulse pressure calculated from conventional BP readings. Extrapolation from the Cox regression model showed that at any given level of 24-h systolic BP, the cardiovascular risk increased with lower 24-h diastolic BP and hence with higher pulse pressure. In contrast, ambulatory mean pressure was not correlated with outcome.

Our observations are in line with the growing body of

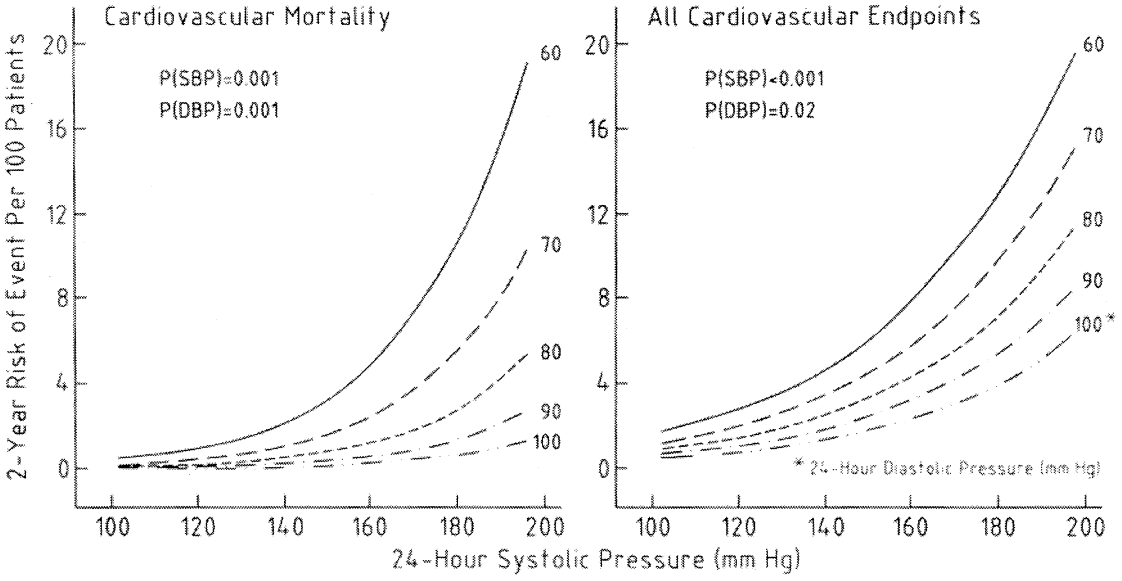

FIG. 1. Risk of cardiovascular death or cardiovascular end point associated in all patients with 24-h systolic pressure (SBP) at entry at fixed levels of 24-h diastolic pressure (DBP). The 2-year probability of an event was standardized to placebo treatment, female sex, 69.6 years (mean age), no previous cardiovascular complications, and nonsmoking.

evidence[4–11] proving that, especially in older people, pulse pressure measured by conventional sphygmomanometry is an independent risk factor. In the Framingham Heart Study there was, with increasing age, a shift from diastolic pressure to systolic pressure and then to pulse pressure as predictors of cardiovascular risk.[9] At less than 50 years, diastolic pressure was the strongest predictor. Age 50 to 59 years was a transition period when all three BP indexes were comparable predictors, and from 60 years on, diastolic pressure was negatively related to the risk of coronary events, therefore pulse pressure became superior to systolic pressure.[9] To the best of our knowledge, only a few studies[12,13] reported on ambulatory pulse pressure as a predictor of cardiovascular risk. Khattar of the Northwick Park Hospital group kept 140 hypertensive patients (mean age, 57.9 years), who at baseline had been subjected to 24-h ambulatory intraarterial monitoring, in follow-up for 9.4 years.[12] Pulse pressure behaved as the strongest independent predictor of left ventricular mass index, carotid intima–media thickness, and carotid artery cross-sectional area, accounting for the influences of both systolic and diastolic BP.[12] Verdecchia and co-workers[13] followed 2010 initially untreated subjects with uncomplicated essential hypertension (mean age, 51.7 years) for 3.8 years. In thirds of the distributions of the office and 24-h pulse pressures, the rates of cardiovascular events expressed in cases per 100 patient-years were 1.38, 2.12, and 4.34 ($P < .01$ for trend) and 1.19, 1.81, and 4.92 ($P < .01$), respectively. With adjustment for white-coat hypertension and nondipper status, ambulatory pulse pressure was associated with the greatest reduction in the -2 log likelihood statistics for cardiovascular morbidity ($P < .05$ *v* office pulse pressure).[13] These findings are in line with our observation that the 24-h and nighttime pulse pressures remained significant predictors of cardiovascular complications in Cox models, which also included conventional pulse pressure as an independent predictor variable.

In keeping with earlier echocardiographic studies[21,22] and the concept of a dynamic interaction between the heart and the large arteries,[3] we found that all types of ambulatory pulse pressures—but not ambulatory mean pressure, conventional pulse pressure, or conventional mean pressure—predicted the increase during follow-up of the Sokolow-Lyon voltage index to a value of 3.5 mV or more. In a case-control study of coronary heart disease, increased left ventricular mass was positively associated with proximal aortic stiffness.[23] In a cross-sectional analysis of the participants enrolled in the Atherosclerosis Risk in Communities study, which was adjusted for age, body weight, and the use of antihypertensive medications, electrocardiographic left ventricular mass was positively and independently correlated with greater pulse pressure and higher mean pressure.[24]

The greater number of measurements, the absence of digit preference and observer bias, and the minimization of the white-coat effect probably contributed to the predictive superiority of ambulatory over conventional pulse pressure. Furthermore, in keeping with established hemodynamic concepts,[3] ambulatory pulse pressure may more accurately reflect the interplay between the heart and the central arteries. Systolic hypertension in the elderly is characterized by stiffening of the large arteries and increased wave reflections from peripheral arterial sites.[3] In line with this concept, we found that the conventional and ambulatory pulse pressures were independently and inversely correlated with body height. Shorter stature decreases the distance over which reflected waves have to

travel and increases the probability that the forward and reflected waves coincide to jointly increase systolic pressure.[21] Exaggerated increases in BP in response to physical activity or stress are more likely to occur in older patients with stiff arteries and, by way of the baroreceptor reflex, may produce transient decreases in heart rate. During conventional BP measurement in the sitting position or at night, these reflex mechanisms may not be activated. Consequently, for conventional and nighttime BP measurements, there was no correlation between pulse pressure and heart rate. However, in whole-day and daytime ambulatory recordings an inverse association between pulse pressure and pulse rate was evident.

In the active treatment group compared with the patients randomized to placebo, the relation between outcome and ambulatory pulse pressure was attenuated to a nonsignificant level. The point estimates of the relative hazard rates were of the same order of magnitude as those in the placebo group, but due to the smaller number of events the confidence intervals were wider and included unity. Any antihypertensive drug that reduces arteriolar tone and therefore, mean pressure may decrease pulse pressure through a passive increase in arterial compliance.[2] A reduction of the ventricular ejection rate or active relaxation of vascular smooth muscle cells may specifically reduce systolic pressure and pulse pressure.[2] We found that active therapy, which in nearly 90% of the patients consisted of nitrendipine given alone or in combination with other study medications, reduced the conventional and ambulatory pulse pressures by 4 to 6 mm Hg. Nitrendipine has a high selectivity for the vasculature and increases the elasticity of the large arteries over and beyond what can be expected on the basis of BP lowering alone.[16,25]

In conclusion, in older patients with isolated systolic hypertension higher pulse pressure estimated by 24-h ambulatory monitoring is a better predictor of adverse outcomes than conventional pulse pressure, probably because it more accurately reflects the dynamic interaction between the heart and the large arteries. In contrast, ambulatory and conventional mean pressures are not correlated with a worse outcome.

Appendix

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